derivative to an ε-aminolysyl group of Keyhole Limpet Hemocyanin, and wherein the C-4 carbon is present in a CH_2 group, so as to stimulate or enhance production of an antibody to GM2 and GD2 in the subject, whichever is present as a derivative in the conjugate, and thereby delay recurrence of melanoma in said subject at risk of relapse of said melanoma.--

REMARKS

Claims 78, 80-92, 94 and 96-99 are pending in the application. These claims have all been cancelled without disclaimer or prejudice to applicants' right to pursue patent protection for the subject matter thereof in a subsequent application. New claims 100-126 are submitted herewith for the Examiner's review and consideration. These claims are completely supported by the application as filed (see below) and thus they raise no issue of new matter. Therefore, entry of this Amendment into the file of the application is respectfully requested such that claims 100-126 will be pending.

In particular, support for the new claims 100-126 may be found, *inter alia*, in the specification as follows: claim 100: page 5, lines 4-7, page 11, lines 13-15, page 32, lines 1-20, page 65, lines 9-15, page 76, lines 19-21 and Figure 1; claim 101: page 12, lines 15-16; claims 102-107: page 13,. lines 8-26; claims 108-110: page 14, lines 1-5; claim 111: page 53, line 35 to page 54, line 4; claim 112: see support for claims 100-111; claim 113: pages 77-78 and the Experimental Results; claim 114: page 5, lines 4-7, page 11, lines 13-15, page 15, lines 11-22, page 32, lines 1-20, page 65, lines 9-15, page 76, lines 19-21 and Figure 1; claim 115: page 5, lines 4-7,

page 11, lines 13-15, page 15, line 26 to page 16, line 20, page 32, lines 1-20, page 65, lines 9-15, page 76, lines 19-21 and Figure 1; claims 116-118: page 17, lines 5-10; claims 119-120: page 18, lines 5-10; claims 121-122: page 55, lines 10-14; claim 123: page 93, lines 1-3; claim 124: page 54, lines 19-21, page 66, lines 4-14 and page 87, lines 27-30; claim 125: page 54, lines 19-21; and claim 126: pages 77-78 and the Experimental Results.

Objection to the Disclosure

The Examiner stated in ¶4 on page 2 of the Office Action that the prior objection to the disclosure is maintained for the reasons as set forth in the Office Action mailed June 10, 1996 (Paper No. 9). The Examiner further stated that applicants submit that they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner additionally stated that until applicants submit a proper Figure, the objection is maintained.

In response to the above Objection, applicants submit they will provide a new Figure 6B upon the indication of allowable subject matter.

Obviousness-Type Double Patenting Rejection

The Examiner has provisionally rejected claims 78, 80-92 and a 94-99 as being unpatentable due to obviousness-type double patenting over claims 78-93 and 95-100 of copending Application No. 08/475,784 for the reasons made of record in Paper No. 23, mailed October 5, 1999 and Paper No. 25, mailed June 19, 2000. The Examiner stated that applicants argue that the claims of 08/475,784 do not render obvious the instant claims. The Examiner stated that applicants' arguments filed June 10, 1996 have been fully considered but they are not

persuasive because applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

The Examiner has also provisionally rejected claims 78, 80-92 and 94-99 as being unpatentable due to obviousness-type double patenting over claims 109-122 of copending Application No. 08/477,147 for the reasons made of record in Paper No. 23, mailed October 5, 1999 and Paper No. 25, mailed June 19, 2000. The Examiner stated that applicants argue that the claims of 08/477,147 do not render obvious the instant claims. The Examiner additionally stated that applicants' arguments filed June 10, 1996 have been fully considered but they are not persuasive because applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

The Examiner has additionally provisionally rejected claims 78, 80-92 and 94-99 as being unpatentable due to obviousness-type double patenting over claims 97-99, 101-111 and 113-118 of copending Application No. 08/196,154 for the reasons made of record in Paper No. 23, mailed October 5, 1999 and in Paper No. 25, mailed June 19, 2000. The Examiner stated that applicants argue that the claims of 08/196,154 do not render obvious the instant claims. The Examiner additionally stated that applicants' arguments filed June 10, 1996 have been fully considered but they are not persuasive because applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

The provisional double-patenting rejections of claims 78, 80-92 and 94-99 of the present application over application Serial Nos. 08/475,784; 08/477,147 and 08/196,154 are respectfully traversed. In response to these rejections, applicants submit that M.P.E.P. §804 IB, in discussing

provisional double-patenting rejections between copending applications, requires that the:

> 'provisional' double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in one of the applications. If the 'provisional' double patenting rejection in one application is the only rejection remaining in the application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the 'provisional' double patenting rejection in the other application into a double patenting rejection at the time one application issues as a patent. (emphasis supplied by applicants).

Applicants submit, therefore, for the reasons discussed below, that new claims 100-126 are believed to distinguish the invention over all of the references cited by the Examiner to reject claims 78, 80-92, 94 and 96-99, which rejections should therefore be withdrawn. Following such withdrawal, the only remaining rejection in this application would be the provisional double-patenting rejection of the claims. In accordance with the M.P.E.P. section quoted above, the provisional double patenting rejection should thus be withdrawn to permit the application to issue as a patent. Such action is therefore respectfully solicited.

Claim Rejections Withdrawn

Applicants note with appreciation the Examiner's statement in ¶8 at page 4 of the Office Action that the rejection of claims

78-92, 94 and 96-99 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, is withdrawn.

Applicants additionally wish to express their appreciation for the Examiner's statement in ¶9 on page 4 of the Office Action that the rejection of claims 78-92, 94 and 96-99 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2: 401-409, 1991), Liane et al. (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol. 182:32-43, 1990), Kensil et al. (The Journal of Immunology, 146(2):431-437, 1991), Marciani et al. (Vaccine,9:89-96, 1991), and Uemura et al. (J. Biochem., 79(6):1253-1261, 1976) is also withdrawn.

New Grounds of Rejection

The following new grounds of rejection are set forth by the Examiner in the Office Action.

In ¶10 of the Office Action, claims 78 and 80-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al U.S. Patent No. 5,599,914 issued February 4, 1997, filed November 24, 1989 ("Wiegand") in view of Fiume et al., Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 256-284, 1988 ("Fiume"), Ritter et al., Seminars in Cancer Biology, 2:401-409, 1991 ("Ritter"), Kensil et al., The Journal of Immunology, 146(2):431-437, 1991 ("Kensil"), Marciani et al., Vaccine, 9:89-96, 1991 ("Marciani") and Uemura et al., J.

Biochem., 79(6):1253-1261, 1976 ("Uemura").

With regard to the above-described rejection the Examiner stated in the Office Action that Wiegand discloses modified glycosphingolipids (GM3, GD3, GM2 and GM1). The Examiner stated that Wiegand discloses a method for chemical modification of the sphingoid portion of glycosphingolipids to make glycosphingolipids capable of coupling to proteins, citing to the Abstract of the disclosure. The Examiner stated that Wiegand discloses that the method of chemical modification is that of ozonolysis at the C-4 double bond of the sphingosine base, resulting in the formation of a reactive aldehyde species (citing to col. 2, line 43 to col. 3, line 67). The Examiner stated that Wiegand discloses that the aldehyde group is susceptible to reductive amination. The Examiner stated that Wiegand fails to disclose conjugation of the modified glycosphingolipid to KLH via an amine linkage between the C-4 carbon of sphingosine base and an ε-aminolysyl group of KLH. The Examiner additionally stated that Wiegand also fails to disclose a composition that comprises a saponin derivable from the bark of the Quillaja saponaria Molina tree (i.e., QS-21).

The Examiner additionally stated that Fiume (1988) teaches that reductive amination of reactive aldehyde species with proteins having ε-lysine groups is well known in the art (citing to pps. 268-269). The Examiner stated that specifically, Fiume teaches that an aldehyde group of a galactosyl residue may be reacted with an ε-lysine of a protein.

The Examiner also stated that Ritter (1991) teaches that IgG responses to gangliosides may be increased by the covalent

attachment of foreign carrier proteins such as KLH to the gangliosides, resulting in the T-cell help necessary for the response (citing to p. 406, ¶1). The Examiner stated that Ritter teaches that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated toxicity, and d) is generally detectable in the serum for longer periods after immunization.

The Examiner further stated that Kensil et al. teach that QS-21, i.e., the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree, produced a higher antibody response than conventional aluminum hydroxide (citing to p. 433, column 2, ¶4, and Figure 3). The Examiner stated that Kensil et al. also teach that the immune response obtained with QS-21 reached a plateau at doses between 10-80 µg in mice (citing to p. 433, column 1, ¶3).

The Examiner then stated that Marciani et al. teach that QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (citing to p. 94, ¶1).

The Examiner additionally stated that Uemura et al. teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

The Examiner therefore concluded that it would have been *prima facie* obvious to one of ordinary skill at the time the invention was made to have used the modified sphingolipids of Wiegand to make glycoconjugates that are the same as those claimed. The Examiner stated that Wiegand teaches a modified

glycosphingolipid that has a reactive aldehyde group (at the C-4 position of the sphingosine base) that may be used for coupling to proteins as taught by Fiume, because Fiume demonstrates that methods of reductive amination to link proteins, via ε-lysine residues, to reactive aldehyde groups, is known in the art. The Examiner stated that because Wiegand teaches a method of ozonolysis which results in the formation of a reactive aldehyde species, the bond that would be formed between the C-4 carbon of the sphingosine base and the KLH would be an amino linkage that would cause the C-4 carbon to be present in a CH2 group. The Examiner went on to state that it would have been further *prima facie* obvious to one of ordinary skill in the art to have used KLH as the protein carrier because, as Ritter teaches, attachment of gangliosides to carrier proteins such as KLH increase IgG responses to gangliosides. The Examiner then stated that it would have been *prima facie* obvious to one of ordinary skill in the art to add QS-21 because, as taught by Kensil, it provides for a higher antibody response, and QS-21 provides the advantages that it is not toxic to animals (citing to the Marciani reference). The Examiner additionally stated that it also would have been *prima facie* obvious to optimize the doses of QS-21 in the composition, and also that it would have been *prima facie* obvious to one of ordinary skill in the art to optimize the weight ratio of the components of the composition to provide an optimal response.

The Examiner further stated that one would have reasonably expected the conjugation procedure to work as substituted because conjugation through the ε-aminolysyl groups of carrier proteins for enhanced immunogenicity is routine in the art and, as Uemura teaches, ozonolysis and reduction of various sphingolipids does not affect the haptenic reactivity with

antibodies.

Applicants respectfully traverse this new ground of rejection. The invention recited in the new claims 100-126 submitted herewith is not suggested to one of ordinary skill in this field of art by the disclosure of the above-cited references, whether they are taken alone or in combination, for the reasons set forth below.

Turning first to Wiegand, the subject reference is directed to the chemical modification of the sphingoid portions of glycosphingolipids and the subsequent coupling of such modified glycosphingolipids to other molecules, such as proteins. The glycosphingolipids useful in the process disclosed by the reference, however, are disclosed in a generic fashion with no teaching or suggestion that any particular species within this genus would perform more effectively than any other, i.e., when linked to form an immunoconjugate composition such as is taught and claimed in the present application. This broad scope of disclosure is specifically demonstrated in, for example, Example B of the reference (commencing at column 5), which describes, *inter alia*, the preparation and subsequent coupling of reductively aminated ozonolysis products of the gangliosides GM3, GD3, GM2 and GM1. No particular ganglioside is described as being preferred or as performing any more effectively than any of the other gangliosides falling within the scope of the reference. In particular, there is no teaching or suggestion that the modification and conjugation of, specifically, either the GM2 or the GD2 ganglioside (as specifically recited in applicants' new independent claims) would produce a composition having properties superior in any fashion to those obtained with the use of any other(s) of the gangliosides

falling within the scope of the genus of glycosphingolipids disclosed in the reference.

Several additional features which further distinguish the invention from the Wiegand reference are pointed out by the Examiner herself in the Office Action. In particular the Examiner stated (as noted above) on p. 5 of the Action that: (i) Wiegand fails to disclose conjugation of the modified glycosphingolipid to KLH, (ii) Wiegand fails to disclose conjugation via an amine linkage between the C-4 carbon of sphingosine base and an ε-aminolysyl group of KLH, and (iii) Wiegand also fails to disclose a composition that comprises a saponin derivable from the bark of the Quillaja saponaria Molina tree (i.e., QS-21).

The presently claimed invention is thus distinguishable and therefore patentable over Wiegand on several grounds, as summarized below. First, the Wiegand reference contains no teaching or disclosure which would suggest to one of ordinary skill in this art to use, in particular, the GM2 or the GD2 ganglioside derivative specifically recited in applicants' claims, in an immunoconjugate of the present invention. Second, there is no disclosure in the Wiegand reference which teaches or suggests the conjugation of a (modified) glycosphingolipid with Keyhole Limpet Hemocyanin ("KLH"), i.e., the specific immunogenic protein recited in claims 100-126 now pending in the application. That is, the only particular example of such a protein disclosed in Wiegand is human serum albumin ("HSA") (see, e.g., col. 5, lines 25-30). Third, there is no disclosure in Wiegand which would suggest the formation of a GM2 (or GD2)-KLH-QS21 conjugate. As noted above, the Office Action states (see p. 5) that Wiegand fails to disclose a composition that comprises a saponin derivable

from the bark of a Quillaja saponaria Molina tree, i.e., QS-21. Fourth, it is not obvious from the disclosure of the reference that a vaccine comprised of a conjugate of a GM2 or GD2 ganglioside derivative coupled to KLH, and a saponin derivable from the bark of a Quillaja saponaria Molina tree would provide a superior immunogenic effect in human cancer patients.

More particularly, with regard to the issue whether it would be obvious to one of ordinary skill in this art to couple a GM2 or GD2 ganglioside derivative to KLH, the Examiner as noted above stated in the Office Action that Wiegand does not teach or suggest such a construct. The Examiner thus has cited the Ritter reference in an effort to supply this missing element. There is, however, no teaching in either the Wiegand reference or the Ritter reference to suggest the combination of their disclosures. The references, moreover, teach away from such a combination in that while Wiegand does disclose the conjugation of a modified glycosphingolipid to a carrier, the particular carrier taught for use with the invention is human serum albumin ("HSA"), see, e.g., Example B at col. 5, lines 24-28. In contrast, Ritter discloses the use of Keyhole Limpet Hemocyanin ("KLH") as the immunogenic carrier protein. There is thus no support for the Examiner's proposed combination of Wiegand and Ritter.

Further to the above, there is no also no disclosure contained in the remaining cited references to suggest to one of ordinary skill in this art the formation of a GM2 (or GD2)-KLH conjugate in combination with QS-21. The Examiner acknowledged in the Office Action (see p. 5) that Wiegand fails to disclose a composition comprising a saponin derivable from the bark of the Quillaja saponaria Molina tree. Ritter also contains no

such disclosure. The Examiner thus cited the Kensil and Marciani references for their disclosure (noted above) concerning QS-21. Neither of these references, however, discloses the conjugation of a modified ganglioside derivative with an immunogenic protein carrier such as KLH. Moreover, as demonstrated by the Experimental Results described in the present application, the inclusion of the QS-21 adjuvant in the claimed composition provides unexpectedly improved results over those obtained with the use of other known adjuvants. Applicants submit, therefore, that these improved results evidence that the inclusion of the QS-21 adjuvant in a composition comprising the GM2 or GD2 ganglioside-KLH conjugate would not be obvious to one of ordinary skill in this art.

In summary, therefore, as recognized by the Examiner in her Office Action and as further established by the arguments provide herein, the combination of Wiegand with any or all of the Ritter, Kensil and Marciani references neither teaches nor suggests the formation of a GM2 or GD2-KLH conjugate in combination with QS-21, utilizing the specific mode of linking the conjugate together as recited in the claims. For this reason, the invention as presently claimed is believed to patentably distinguish over the cited references.

Moreover, the Experimental Results portion of applicants' specification conclusively demonstrates that the presently claimed composition incorporating GM2 or GD2 ganglioside derivatives is very successful in stimulating or ennancing the production of antibodies in human subjects so as to treat and/or prevent cancers, particularly melanoma, in such human subjects. Such a result could not have been predicted from the cited art. Applicants attach hereto as **Exhibit A** a copy of a

paper by Ragupathi, et al., "Induction of Antibodies Against GD3 Ganglioside in Melanoma Patients By Vaccination With GD3-Lactone-KLH Conjugate Plus Immunological Adjuvant QS-21", Int. J. Cancer:85, 659-666 (2000). Exhibit A clearly demonstrates that compositions based on the GD3 ganglioside-KLH+QS-21 are **NOT** effective in stimulating the production of GD3 antibodies in humans. In particular, the authors stated, at p. 665, second column, ¶2, lines 18-19, that, "GD3-KLH failed to induce antibody against GD3". (emphasis supplied by applicants). Applicants submit, therefore, that the improved results obtained with the GM2 or GD2 ganglioside derivatives conjugated to KLH as recited in the claims + QS-21, in contrast to the poor results achieved with a comparable GD3-KLH conjugate + QS-21, as described by the authors of the subject Exhibit, provide convincing evidence that the presently claimed invention would **NOT** be obvious to one of ordinary skill in this art over the cited references, whether such references are taken alone or in any combination.

Applicants therefore submit that for the preceeding reasons the invention as presently claimed is distinguishable over the Wiegand, Ritter, Kensil and Marciani references cited in combination to reject claims 78 and 80-91. Whether the references are taken individually or in combination, the arguments above clearly support applicants' position that the invention as presently claimed is not obvious over the disclosure of the cited prior art.[1,2] Moreover, as discussed in

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1 The Fiume reference cited by the Examiner in combination with the other references discussed above to reject the claims relates to the placement of an aldehyde derivative on the sugar portion of a sphingolipid and linking this structure to an ε-amino group of lysine located upon a protein. The Examiner's suggestion on p. 5 of the Office Action that Fiume has a more generic teaching, i.e., that it teaches that reductive amination of reactive proteins having ε-lysine groups is well-known in the art is not supported by the disclosure of the reference, which is limited to the chemistry of sugar-based compositions. Moreover, as shown, for example, in the paper by Ritter, et al. attached hereto as **Exhibit B**, entitled "Antibody Response to Immunization With Purified GD3 Ganglioside and GD3 Derivatives (Lactones, Amide and Gangliosidol)

the footnotes below, neither the Fiume nor the Uemura references, cited by the Examiner in combination with the Wiegand, Ritter, Kensil and Marciani references to reject claims 78 and 80-91, supply the elements missing from the above-discussed references in a manner so as to render the invention as now claimed obvious to one of ordinary skill in this art. The Examiner is thus respectfully requested to reconsider and withdraw her rejection of claims 78 and 80-91 based on the references discussed above.

In ¶11 of the Office Action, claims 78, 92, 94 and 96-99 were rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand, Fiume, Livingston et al., Cancer Research, 149:7045-7050, 1989 ("Livingston") in view of Ritter, Livingston et al. U.S. Patent No. 5,102,663 ("Livingston '663 patent"), Kensil, Marciani and Uemura.

With regard to this rejection, the Examiner stated that, as discussed in ¶10 of the Office Action, Wiegand in combination with Fiume teaches a glycoconjugate as claimed in claim 78.

The Examiner additionally stated that Livingston teaches that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (citing to p. 7048, ¶1 and column 2, ¶2). The Examiner stated that

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in the Mouse", Immunobiol.:182, 32-43 (1990) it was well known in the art that at least as of the date of the reference the conjugation of ganglioside derivatives through the sugar portion did not provide an composition effective for stimulating or enhancing the production of antibodies (see, e.g., Table I on p.34).

2 Further according to the Examiner (at p. 6 of the Office Action) the Uemura reference additionally cited in combination with the other above-discussed references to reject the claims teaches that the ozonolysis and reduction of various sphingolipids did not affect the haptenic activity of the ganglioside derivative with antibodies. The Ragupathi et al. reference attached as **Exhibit A**, however, demonstrates that the Examiner's statement is not generally correct, since the GD3-based conjugate, formed with ozonolysis and reduction of the sphingolipid , "[f]ailed to induce antibody against GD3" (see p. 665), thus demonstrating that haptenic activity of certain sphingolipids can be negatively affected by such ozonolysis and reduction.

Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (citing to p. 7047, paragraph bridging columns 1-2). The Examiner additionally stated that Livingston et al. also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (citing to p. 7045, column 1, ¶2).

The Examiner stated that Ritter (1991) teaches that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T-cell help necessary for the response (citing to p. 406, ¶1). The Examiner stated that Ritter discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissue, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, and d) is generally detectable in the serum for longer periods after immunization.

The Examiner stated that the Livingston '663 patent teaches that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell membrane components of melanoma and other tumors of neuroectodermal origin (citing to column 1, lines 22-28).

The Examiner stated that Kensil et al. teach that QS-21 (i.e., the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response then conventional aluminum hydroxide (citing to p. 433, column 2, ¶4 and Figure 3). The Examiner also stated that Kensil et al. also teach that the immune response obtained with QS-21 reached a plateau at doses between 10-80 µg in mice (citing to p.433, column 1, ¶3).

The Examiner further stated that Marciani et al. teach that QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (citing to p. 93, ¶1).

The Examiner next stated that Uemura et al. teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic activity of the ganglioside derivative with antibodies.

The Examiner then stated that it would have been *prima facie* obvious to one of ordinary skill at the time the invention was made to have used the modified glycosphingolipids of Wiegand to make glycoconjugates that are the same as those claimed, and then to have used the glycoconjugates in compositions for stimulating or enhancing antibody production or in a method of treating cancer, because Livingston teaches that melanoma recurrence is delayed in patients developing GM2 antibodies after treatment with vaccines comprising GM2 (citing to p. 7048, ¶1 and column 2, ¶2). The Examiner stated that Livingston et al. teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (citing to 7047, paragraph bridging columns 1-2). The Examiner stated that Livingston et al. also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (citing p. 7045, column 1, ¶2). The Examiner stated that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have added QS-21 as an adjuvant to the GM2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al. (1991), thus providing the advantages of Ritter et al. and, as Kensil teaches, adding the QS-21 is

advantageous because it provides for a higher antibody response than the commonly used adjuvant. The Examiner additionally stated that QS-21 provides the advantage that it is not toxic to animals (citing to the Marciani reference).

The Examiner then went on to state that it also would have been *prima facie* obvious to optimize the doses of QS-21 in the composition and that would have additionally been *prima facie* obvious to one of ordinary skill in the art to optimize the weight ratio of the components of the composition to provide an optimal response.

The Examiner next stated that one would have reasonably expected the conjugation procedure to work as substituted because conjugation through the ε-aminolysyl groups of carrier proteins for enhancing immunogenicity is routine in the art and, as Uemura teaches, ozonolysis and reduction of various sphingolipids does not affect the haptenic activity with antibodies.

The Examiner further stated that it also would have been *prima facie* obvious for one of ordinary skill in the art to substitute any one of GM3, GD2, GD3 or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined *supra* because they are all prominent cell-membrane components of melanomas as taught by the Livingston '663 patent. The Examiner also stated that optimization of the dosage, the route of administration, number of sites of immunization to administer the composition is well within the skill of the ordinary artisan.

The Examiner stated that one would reasonably have expected the conjugation procedure to work as substituted because

conjugation through the ε-aminolysyl groups of carrier proteins for enhanced immunogenicity is routine in the art and Uemura et al. teach that ozonolysis and reduction of various sphingolipids did not affect the haptenic activity with antibodies.

Applicants respectfully traverse the above-cited ground for rejection of claims 78, 92, 94 and 96-99. In the discussion above with respect to the previous ground of rejection, applicants established that their invention is patentably distinguishable over six of the eight references cited in combination to reject claims 78, 92, 94 and 96-99, i.e., Wiegand, Fiume, Ritter, Kensil, Marciani and Uemura. The arguments concerning those references, which are specifically incorporated herein by reference, are not repeated here. The two new references in the combination are Livingston et al., Cancer Research, 149: 7045-7050 (1989) ("Livingston") and Livingston et al. U.S. Patent No. 5,102,663 ("the Livingston '663 patent"). As discussed below, neither Livingston, nor the Livingston '663 patent, taken in combination with the other six references discussed above, would have rendered the invention as presently claimed obvious to one of ordinary skill in this field of art.

The Livingston reference was cited by the Examiner for its disclosure (1) concerning the effect of GM2 antibodies on melanoma recurrence, (2) that more patients produced IgM antibodies than IgG antibodies to the GM2, and (3) that the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas. The reference does not, however, provide the elements missing from the disclosure of the six references discussed above, i.e., there is no teaching or suggestion in Livingston to form a composition comprising a

conjugate of a GM2 or GD2 ganglioside derivative to Keyhole Limpet Hemocyanin, in combination with a saponin derivable from the bark of a Quillaja saponaria Molina tree, wherein in the conjugate the ganglioside derivative is covalently bound to the KLH through a C-4 carbon of the ceramide portion of the derivative to the ε-aminolysyl group of the KLH. These features of the invention are found in each of the new independent claims of the application, including method claim 114 directed to a method of stimulating or enhancing production of an antibody using a GM2 or GD2 derivative, claim 115 directed to a method of treating a cancer in a subject and claim 126 directed to a method of delaying recurrence of melanoma in subjects at risk of relapse of melanoma, but are not found within the cited reference. Thus, as the Livingston reference fails to provide the elements of the invention missing from the cited prior art, claims 100-126 are believed to distinguish the invention over the reference whether taken alone, or in the combination relied upon by the Examiner.

The Livingston '663 patent teaches that certain gangliosides (i.e., GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3) are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin. In like manner to the Livingston reference discussed above, the subject Livingston '663 patent neither discloses nor suggests the composition set forth in applicants' new claims wherein the conjugate is linked in the manner recited, nor the methods claimed for using the claimed composition for stimulating or enhancing antibody production, for treating cancer, and for preventing the relapse of melanoma in subjects at risk of such relapse. Therefore, the invention as recited in applicants' new claims is clearly patentably distinct over the Livingston '663 patent taken alone or in combination with the other cited references relied

upon by the Examiner. The Examiner is thus respectfully requested to reconsider and withdraw the rejection of claims 78, 92, 94 and 96-99 based upon the cited combination of references.

In ¶12 of the Office Action, claim 95 is rejected under 35 U.S.C. 103(a) as unpatentable over Wiegand, in view of Fiume, Livingston, Ritter, Livingston '663 patent, Kensil, Marciani and Uemura as applied to claims 78, 80-92 94 and 96-99 and further in view of Irie et al. U.S. Patent No. 4,557,931 ("the Irie '931 patent").

With regard to this rejection, the Examiner stated that the teachings of Wiegand, Fiume, Livingston, Ritter, the Livingston '663 patent, Kensil, Marciani and Uemura are already discussed in the Office Action. The Examiner stated that the combination differs [i.e., from the invention] by not teaching the administration of the composition for treating cancer of epithelial origin. The Examiner stated that Irie teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanomas and breast carcinomas (citing to column 1, lines 28-31).

The Examiner stated that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the GM2-KLH conjugate/QS-21 composition as combined *supra* to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e., breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Irie and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

Applicants respectfully traverse this rejection for the reasons provided below. The newly cited reference relied upon in the rejection of claim 95 is the Irie '931 patent. Each of the other references cited in combination with the Irie '931 patent to reject applicants' claim 95 is discussed and distinguished above. Thus these arguments are not repeated here, although they are specifically incorporated into this discussion by reference thereto.

The Irie '931 patent is cited, as noted above, for its disclosure that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanomas and breast carcinomas. This cited reference, however, does not provide the elements missing from the references discussed above, i.e., it does not disclose or suggest the claimed composition comprising a conjugate covalently bound as recited in the claims, and also including a saponin derivable from the bark of a Quillaja saponaria Molina tree, or the method of using such composition to enhance or stimulate antibody production, to treat cancer, or to prevent relapse of melanoma in patients at risk of such relapse. For this reason the present claims (nos. 100-126) are believed to patentably distinguish over the Irie '931 patent, taken alone or in the combination relied upon by the Examiner to reject claims 78,80-91, 92, 94 and 96-99. The Examiner is thus respectfully requested to reconsider and withdraw the rejection of claim 95 under 35 U.S.C. 103(a).

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection set forth in the Office

Action and earnestly solicit allowance of the now pending claims, i.e., new claims 100-126.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' attorneys invite the Examiner to telephone either of them at the number provided below.

A fee of $42.00 is believed to be due for the addition of an additional independent claim. In addition, as noted above, a fee of $465.00 is believed to be due for a three month extension of time for filing this response. Thus, a check totaling $507.00 which includes these two fees is enclosed herewith. If any additional fees are required, authorization is hereby given to charge the amount of the required fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Mark A. Farley 2/27/03
John P. White Date
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